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Management of focal segmental glomerulosclerosis: Evidence-based recommendations

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Management of focal segmental glomerulosclerosis: Evidence-based recommendations. Focal segmental glomerulosclerosis (FSGS) is a diagnosis based on the presence of glomeruli with segmental scarring in association with intracapillary foam cells and adhesions. To develop evidence-based treatment guidelines, a MEDLINE search was conducted, and articles were reviewed using levels of evidence. Graded recommendations were developed according to the level of evidence. There was limited evidence found on which to develop recommendations.

Treatment with prednisone of 0.5 to 2 mg/kg/day should be considered in all patients and continued for six months before declaring the patient resistant to therapy. Remission is associated with the use of high doses (more than 60 mg/day) for three months; therefore, if there is a concern about prolonged use, a reduction in dose to 0.5 mg/kg/day should be made only after three months (grade D).

The use of cyclosporine A (CsA) at doses to maintain serum levels at 150 to 300 μg/ml may be effective in reducing urinary protein excretion. Relapse after reducing or stopping CsA is very common. Long-term use may be required to maintain remission (grade D).

The use of cytotoxic therapy (cyclophosphamide, azathioprine, and chlorambucil) for adults is second-line therapy (grade D).

Plasmapheresis or protein adsorption may be recommended for renal transplant patients with recurrent FSGS (grade D).

In 1957, Rich originally reported focal segmental glomerulosclerosis (FSGS) from a postmortem study of 20 children with nephrotic syndrome [1]. He described glomerulosclerosis, focal and segmental in location, developing initially in juxtamedullary glomeruli and progressing to involve all glomeruli. Subsequently, there have been detailed descriptions of what may be variants of FSGS or different stages in the evolution of the glomerulopathy. The prevalence of FSGS among patients with glomerulonephritis varies with the indications for renal biopsy at different institutions from 2.5 to 18.7% of patients undergoing renal biopsy for all causes [2, 3] or 7 to 12% for those with proteinuria [4, 5]. The etiology is unknown, and for reasons that are unclear, the prevalence of primary FSGS appears to be increasing [2].

Key words: sclerosis, segmental scarring, prednisone, cyclosporine A, recurrent FSGS.

NATURAL HISTORY

In adults, FSGS presents with asymptomatic proteinuria in approximately half of the cases and with features of the nephrotic syndrome in half. Hypertension and a reduction in renal function are also commonly seen. In approximately one third of the cases, microscopic hematuria is present, even in the absence of urinary or respiratory tract infection [3, 4]. The clinical course of this condition varies. In patients who have had a treatment-induced complete remission, the course of disease appears to be stable. In patients who have been treated but have not had a remission, there is deterioration of renal function, with a large portion of patients (30 to 63%) developing renal failure [6–11]. Untreated nephrotic patients have been described as having an outcome similar to those who failed a trial of therapy. Untreated non-nephrotic patients may have a better outcome than the untreated nephrotic patients, but reports are mixed in this patient population. However, follow-up in retrospective studies usually extends to only two to five years, and this may not be adequate in such a heterogenous condition.

Negative prognostic indicators are similar to those in other glomerular diseases: an increased serum creatinine level at diagnosis and interstitial scarring on renal biopsy [11]. Two other indicators—nephrotic range proteinuria and hypertension—are not cited consistently [7–9, 11, 12]. These indicators do not forecast which patients will respond to therapy but do predict long-term outcome [11].

Some patients have a malignant clinical course with rapid deterioration in renal function and are unresponsive to therapy [12]. Recurrence in renal allografts in this population is common (15 to 55%) [12–14].

DEFINITIONS

Renal biopsy findings

Terms used in renal pathology must be clear to ensure appropriate referencing. The term focal means that only some glomeruli in the biopsy are involved, whereas segmental refers to involvement of only some lobules of any given glomerulus. Global sclerosis refers to the total involvement of one entire glomerulus. Variants of the disease exist: diffuse mesangial hypercellularity, tip lesion (the segmental lesion is adjacent to the epithelial cells of the early proximal tubule and to the tubular pole of Bowman's capsule), capillary collapse, and focal glomerular obsolescence. Biopsy findings similar to idiopathic FSGS are found secondary to known etiologic agents such as human immunodeficiency virus (HIV) or heroin. These and other forms of secondary FSGS must be ruled out when patients are to be included in studies or clinically treated [2].

Clinical status

The definitions for complete and partial remission often differ between authors. A complete remission may mean reduction of urinary protein excretion to zero, less than 250 mg, or less than 300 mg/day, whereas partial remission may refer to a reduction of daily proteinuria to 0.3 to 2.0 g/day, or a reduction to below nephrotic-range proteinuria. Similarly, definitions of renal insufficiency differ, for example, a serum creatinine of more than 1.5 mg/dl, a creatinine clearance of less than 0.8 ml/seconds, or a doubling of serum creatinine. Regardless of the variance of these definitions for these terms across articles, the outcomes appear to be consistent.

METHODS

Evidence was initially compiled with a MEDLINE literature search using a primary search technique for review and clinical research articles. Secondary searches were done using the reference lists of review articles retrieved initially, and searches of personal files were also done. Published articles were categorized according to design methodology and were reviewed and graded for level of evidence using guidelines published previously by the Canadian Hypertension Society [15]; graded recommendations were developed based on the evidence (Table 1).

Table 1. Levels of evidence

Level 1:	RCT with hard end-point
Level 2:	RCT with surrogate end-point
Level 3:	Non-R trial with a control group, or subgroup analysis of an RCT
Level 4:	Before and after study
Level 5:	Case series >10 patients
Level 6:	Case series <10 patients
Recommendations	
Grade A:	Based upon Level 1 evidence
Grade B:	Based upon Level 2 evidence
Grade C:	Based upon Level 3 evidence
Grade D:	Based upon Level 4 or lower evidence or expert opinion

Abbreviations are: RCT, randomized clinical trial; R, randomized.

MANAGEMENT

Articles describing the clinical course or reporting clinical trials of patients with FSGS often included patients with steroid-resistant, steroid-dependent, or frequently relapsing nephrotic syndrome, without a definitive renal biopsy diagnosis. The studies reviewed in this article are predominantly those including adults with a biopsy-proven diagnosis. Because many reports include other patients (children or patients treated without renal biopsy), the sample size noted in the tables may be smaller than the total reported in the articles. Limiting the review to adult FSGS patients often leaves an inadequate sample size for definitive evidence and lowers the level of evidence [15].

RECOMMENDATIONS

Recommendation 1

Treatment with prednisone of 0.5 to 2.0 mg/kg/day should be considered for patients with FSGS. Treatment should continue for a total duration of six months before declaring the patient steroid resistant. Remission is associated with a dose of at least 60 mg/day. If necessary, the dose may be reduced to 0.5 mg/kg/day, but only after three months (grade D).

Evidence

An overview of the evidence reveals several key findings about prednisone therapy. The dose of prednisone needs to be approximately 60 mg/day initially. The duration of therapy needs to be approximately six months before concluding that the patient is resistant to prednisone therapy; no clinical or biopsy finding predicts the response to therapy. Adults respond as well as children to therapy. Complete remission predicts a good long-term outcome, and nontreatment or lack of response to treatment predicts poor outcome with the development of chronic renal failure (CRF).

A summary of the relevant studies is presented in Table 2 [6–9, 11, 12, 16–18]. There have been no randomized clinical trials of steroid therapy; most reports are case series, with or without controls, and are thus categorized as level 4 or 5 evidence. Most early reports provided few details, if any, on the dose or duration of therapy. Response rates varied tremendously. Lim, Sibley and Spargo reported no responders from 10 FSGS patients

Table 2. Corticosteroid therapy reports

Level of evidence	Author [Ref]	# Adults	Treatment	# Responders/ # treated *remission rate %*	Rate of CRF
Level 4					
	St Hillier [16]	Total 85, NS 30 Non-NS 55	17/30 NS treated Prednisone	16/17 (94%)	
	Beaufils [7]	Total 70, NS 35 Non-NS 35	26/35 NS treated Prednisone	6/20 (23%)	NS 55% Non-NS 9%
	Pei [8]	Total $N = 55$ NS 30 Non-NS 25	Prednisone	7/18 (39%)	No remission 45% Remission 4%
	Rydel [11]	81, NS 60 Non-NS 21	36/60 treated Prednisone	15/30 (50%)	If remission 0% No remission 59% Untreated NS 30%
	Miyata [12]	32 NS	Prednisone	18/32 (56%)	Mesangial hypercellularity associated with poor prognosis
	Nagai [6]	Total $N = 17$ NS 12	8/12 NS treated Prednisone	4/9 (44%)	No treatment or no remission 63%
Level 5					
	Banfi [9]	59 (all NS)	Prednisone $N = 27$ Prednisone ± Cytotoxic $N = 32$	20/27 (74%) 16/32 (50%)	
	Korbet [4]	Total = 46, NS 29 Non-NS 17	16/29 NS treated Prednisone	8/16 (50%)	
	Jenis [17]	Total = 11 NS 9	Prednisone ± Azathioprine	2/6 (33%)	
	Velosa [5]	32	Prednisone	11/26 (42%)	
	Newman [3]	Total = 17, NS 7	Prednisone	3/6 (50%)	
	Lim [18]	10	Prednisone	0/10 (0%)	

receiving prednisone for a median of three weeks [18]. However, Korbet, Schwartz and Lewis reported a 50% response rate (of 16 patients with nephrotic syndrome) and noted that some responses occurred by an average of 3.75 months (range 1 to 10 months), and complete remission occurred at 5.75 to 6.75 months in the three patients who had complete remission [4]. Treatment included 60 mg/day of prednisone for a minimum of one month. In comparing patients who had a remission with those who were not treated or had no response, there was a significant difference in the change in renal function over time that favored the treatment-response group.

In several studies, response rates varied between 2 to 94%, but details on the dose of prednisone and duration of treatment were not included [3, 5, 7, 12, 16, 17].

The importance of dose and duration of therapy and the possibility of physician bias in the undertreatment of adults with FSGS compared with children was put forth by Pei et al in 1987 in a report that included 55 adult patients [8]. Treatment with prednisone (with or without cytotoxic drugs) was given to 18 adult patients. The median duration of treatment was six months. Prednisone dosages varied greatly, from 0.3 to 2 mg/kg/day. Seven adults had complete remissions. The average follow-up was five years, and 96% of the patients who had a complete remission had preservation of renal function, whereas the probability of CRF was 45% in those who had not responded or who were not treated. This level 4 study showed that the probability of remission with a long duration of therapy was as likely in adults (39%) as it was in children (44%) with FSGS and that age was not a factor in treatment response or long-term outcome. Physician bias was likely the reason for only 33% of adults being given a trial of therapy compared with 90% of children.

The same group of investigators reported that the incidence of FSGS was much lower in older patients (more than 60 years) undergoing renal biopsy (17 of 822 biopsies or 2%) even though the prevalence of nephrotic syndrome in patients coming for renal biopsy was similar to younger patients [6]. Of the 17 older patients, 9 had received treatment. Four (44%) achieved complete remission; there were no relapses in those patients who achieved remission (mean follow-up was 37 months), and none of them progressed to renal failure. No untreated patients had a remission, and 9 of the 14 untreated or nonresponders-to-treatment did progress. The treatment that these patients had received was prednisone, alone or combined with cytotoxic therapy, and the maximum dose was 100 mg prednisone alternate days. The mean time to remission was four months. This level 4 study is

consistent with the study results from younger patients in the Toronto Glomerulonephritis Registry reported by Pei et al [8].

In 1995, Rydel et al reported a retrospective assessment of 81 patients, including 60 with nephrotic syndrome [11]. Thirty patients had received treatment, and 15 responded (10 had complete and 5 had partial remissions). Treatment consisted of more than 60 mg/day for a minimum of two months, followed by a tapering schedule. Remission was more common in patients who received a dose of 60 mg/day or more of prednisone for a longer period of time (2.7 vs. 1.5 months for responders and nonresponders, respectively). Remission was not prompt, but most patients did respond by four months of treatment. Prognostic factors associated with the development of CRF were the degree of interstitial fibrosis on renal biopsy and an elevated serum creatinine level at the time of biopsy. These prognostic factors did not predict response to therapy. This level 4 study reinforced that treatment of FSGS with a high dose of prednisone could effect a complete or partial remission in adult patients, but the treatment must be continued for four to six months; attaining remission with treatment was associated with a better long-term prognosis.

A series of 14 patients with collapsing FSGS was reported by Detwiler et al [19]. Only four received treatment with corticosteroids (one of these four also received cytotoxic therapy), and only one had a complete remission (level 6 evidence). A recent study of 43 patients (both children and adults) with collapsing FSGS found that none of the 26 patients treated with prednisone alone benefited. When compared with age-matched controls with classic FSGS, the collapsing variant was more rapidly progressive, with a time course of only 13.0 months to end-stage renal failure compared with 62.5 months (level 5 evidence) [20].

In summary, prednisone treatment at approximately 1 mg/kg or 60 mg/day can induce a remission but must be given for six months before concluding that the patient is steroid resistant.

Recommendation 2

The use of cyclosporine A (CsA) at doses of approximately 5 mg/kg/day may be effective in reducing urinary protein excretion. Relapse after reducing the dose or stopping CsA is very common (grade B). Long-term use of CsA may be required to maintain remission (grade D).

Evidence

Prospective studies have not been conducted to compare corticosteroid therapy with placebo therapy. However, the prospective studies shown in Table 3 were designed to recruit patients who had failed a trial of corticosteroid therapy and to assess the addition or substitution of either a cytotoxic agent or cyclosporine [21–25]. Although CsA can be beneficial in inducing remission, relapse is common after tapering or discontinuing the drug.

Ponticelli reported a prospective trial in which 44 patients with nephrotic syndrome were randomized to CsA or standard therapy [21]. Patients had been classified as steroid resistant if they had no response after six weeks of prednisone therapy. (This definition is not consistent with the current understanding of the time course of response to steroid therapy in FSGS.) A biopsy diagnosis of FSGS was made if one glomerulus with segmental hyalinosis was seen. The treatment group received CsA in two doses per day: 5 mg/kg/day for adults and 6 mg/kg/day for children. Treatment was stopped at six months in nonresponders. For responders, the dose was reduced by 25% every two months so that the drug was ultimately stopped after 12 months. The control group received only supportive therapy. Rescue treatment with corticosteroids was allowed for patients of both groups if there was a rapid decline in renal function. Of the 44 nephrotic patients, only 19 had biopsy-proven FSGS; 10 received CsA, and 9 were in the control group [21]. Three CsA-treated patients attained complete remission, and four had partial remissions. Three patients in the control group had partial remissions, but their diagnoses were not itemized in the report. Relapses were common when the CsA was stopped; only two of the seven responders in the CsA group were in remission at the end of month 12 when CsA was stopped. Follow-up 12 months thereafter was incomplete, but one of the two responders had relapsed to nephrotic range proteinuria; data on the other patient were not reported. Although the probability of attaining remission was greater in the CsA treatment group (0.65 vs. 0.16 for the control group), there was no difference in renal function between the groups at one year. Specific data for the FSGS patients were not presented. In this study, the subgroup of FSGS patients was small (total $N = 19$); the evidence was graded as level 3.

In a later prospective trial, Ponticelli compared CsA with cyclophosphamide. Seventy-three patients with steroid-dependent, frequently relapsing nephrotic syndrome were randomized to CsA for nine months or cyclophosphamide for eight weeks [26]. This study included 11 adults and 55 children with either minimal change disease or FSGS. Not all patients had a renal biopsy for diagnosis, and hence, it is not clear which results are applicable to the adult FSGS patients. Therefore, the evidence relevant to FSGS cannot be assessed and no recommendations can be made.

Open trials of CsA have been reported, but there were small numbers of patients with FSGS (level 4 studies) [22–25]. Lee et al conducted a prospective study with 30 patients, but only five had FSGS [22]. Four responded to CsA therapy, but two relapsed on tapering or with-

Table 3. Cyclosporine A (CsA) studies

Level of evidence	Author [Ref]	# FSGS adults treated	Treatment	Remission on CsA	Remission on control
Level 3					
	Ponticelli [21]	10 treated 9 control	CsA for 12 months vs. supportive	CR 3 adults PR 3 adults	CR 0 PR3[a]
Level 4					
	Lee [22]	5	CsA for 8 months	CR 4	n/a
	Walker [23]	7 adults (total 9)	CsA 4–6 months vs. supportive	CR 0 PR 6[b]	
Level 5					
	Meyrier [24]	46 children	CsA ± Pred	11 (CR + PR)	n/a
Level 6					
	Green [25]	3 adults (total 9)	CsA	CR 1, PR 1	

Abbreviations are: CR, complete remission; PR, partial remission; Pred, prednisone; FSGS, focal segmental glomerulosclerosis.
[a] Diagnosis of responders not reported
[b] Age of responders not reported

drawal of CsA. Walker and Kincaid-Smith reported a randomized cross-over study comparing CsA treatment for four to six months with standard care in nine patients (7 adults) [23]. The standard care for this study included warfarin, which is distinct from control groups in other studies. CsA was given in a dosage of 5 to 10 mg/kg/day. None of the patients had a complete remission, but six had a reduction in urinary protein excretion while on CsA. No patients responded to their standard care. This report did not clarify if the six responders were adults or children. In 1990, Green et al described nine adult patients (three with FSGS) who received treatment with CsA for a maximum of 12 months in twice daily doses (6 to 10 mg/kg/day, mean dose 6.7 mg/kg/day; level 6 evidence) [25]. Two FSGS patients responded: one complete and one partial remission. The third FSGS patient was reported as not having responded after two months of CsA therapy.

In a single report, Meyrier et al combined two open trials with a total of 112 adult patients with nephrotic syndrome [24]. Patients were classified as steroid dependent (6 with FSGS) or steroid resistant (40 with FSGS). In the first study, patients received CsA in two doses daily (5 mg/kg/day). In the second study, patients received low-dose prednisone (0.2 mg/kg/day) and CsA (5 mg/kg/day). At six months, the FSGS patients who were steroid resistant had the lowest response rate (21%). The data on maintenance of remission after withdrawal of CsA were not presented according to diagnosis, and it is unknown if any of the 6 patients with maintained remission out of the 11 patients whose CsA was discontinued had FSGS. Similarly, of the 27 patients followed for a minimum of 12 months, it is not stated how many had FSGS. Although these prospective open studies included 46 patients with FSGS, clear data for this specific subgroup were not presented. Therefore, this report is classified as only level 5 evidence.

Recommendation 3

The use of cytotoxic therapy (cyclophosphamide and chlorambucil) may be considered as second-line therapy (grade D), but the evidence is not conclusive.

Evidence

The few articles regarding the use of cytotoxic agents in adults or children with FSGS are summarized in Table 4 [9, 27–29]. In Banfi et al's retrospective review of FSGS patients with nephrotic syndrome [9], patients were separated into three groups based on treatment received. Group A was treated with prednisone alone. Group B was treated with prednisone 1 mg/kg/day and either chlorambucil, cyclophosphamide, or azathioprine, and Group C was treated with low-dose prednisone therapy (0.2 to 0.3 mg/kg/day) and either azathioprine or cyclophosphamide. Of the 19 patients in group B, 9 had complete remissions, and 2 had partial remissions. Five of the 13 patients in group C had complete remissions. The response rates in the three groups were 74, 58, and 38%, respectively. The author commented that it would not be appropriate to compare the response rates statistically across the three groups, but did state that relapses occurred more frequently in group A and remissions appeared more stable in the two groups that received cytotoxic therapy.

With the dearth of studies with adult patients, three studies involving children were reviewed. Tarshish et al reported a prospective level 1 study [27] comparing prednisone therapy to prednisone combined with cyclophosphamide 2.5 mg/kg/day in 60 children. The response rate was similar in the two groups. Two level 4 studies demonstrated that treatment with cyclophosphamide or chlorambucil was associated with remissions. Geary et al reported on 29 children who received cyclophosphamide for 90 days (at a dose of 2.5 mg/kg/day) [28]; an overall 48% response rate was achieved. Tune et al also

Table 4. Cytotoxic therapy

Level of evidence	Author [Ref]	# Subjects	Treatment	Result	Comment
Level 1					
	Tarshish [27]	60 children	Prednisone vs. prednisone & cyclophosphamide	No difference between therapies	Loss of renal function in 36% and 57% of patients
Level 3					
	Banfi [9]	Total 59 adults Group B = 19 Group C = 13	Prednisone & cytotoxic vs. low dose prednisone and cytotoxic	Group B 58% Group C 38%	Responders to therapy were less likely to lose renal function
Level 4					
	Geary [28]	Total = 29 NS 20	Cyclophosphamide 2.5 mg/kg/day for 90 days	48% overall	1/7 responders vs. 7/8 non-responders developed CRF
	Tune [29]	32 children	i.v./oral steroid & cytotoxic	66% complete remission	

reported an excellent response to cyclophosphamide (2.0 to 2.5 mg/kg/day) or chlorambucil (0.15 to 0.2 mg/kg/day) given for 8 to 12 weeks [29]. Of the 32 children treated, 21 (66%) had a complete remission. However, cyclophosphamide therapy was tested in a randomized clinical trial of 60 children, 30 of whom were randomized to receive cytotoxic therapy. All of the children received concurrent treatment with prednisone. No significant effect was recognized (level 1 evidence). Cameron et al reported a review of 40 patients, including 28 adults, but details of treatment and response were not provided [30]. However, a five-year survival rate of 75% was reported. The conflicting data from these studies make formulation of a recommendation difficult.

Recommendation 4

Plasmapheresis or protein adsorption may be recommended for renal transplant patients with recurrent FSGS (grade D).

Evidence

In some patients, there may be a circulating immunological factor that is associated with recurrence of FSGS in patients who have received a renal allograft [31, 32]. The presence of the circulating factor has been identified by using an *in vitro* assay and calculating permeability of rat glomeruli. Immunoadsorption of plasma proteins has limited temporary effectiveness in reducing urinary protein excretion, with patients rebounding to pretreatment urinary protein excretion rates within three weeks [33, 34]. Plasmapheresis has been attempted in renal allograft recipients with recurrent FSGS with variable results [35, 36]. When used prophylactically in a study of 14 children, half of whom underwent plasma exchange prior to transplantation, recurrence was reduced from four of the six children (66.7%) in the control arm to three of the eight children (37.5%) in the study arm (level 2 evidence) [35]. Recurrence was found to occur within 24 hours of transplantation. In a report of nine patients treated with plasmapheresis for post-transplant recurrence [36], a lasting remission could be attained by instituting treatment immediately; otherwise, remissions were transient (level 6 evidence).

SUMMARY

Studies on the treatment of nephrotic syndrome, either primary treatment or secondary treatment after a failed trial of prednisone, have included patients with FSGS. However, specific information on the FSGS patients is often not clear, and the number of FSGS patients in these trials has been small. No prospective studies have specifically assessed the use of prednisone. Reports of case series support the use of prednisone at an initial dose of 60 mg/day for a minimum of four months; patients should not be considered prednisone resistant until a six-month trial of prednisone has been completed. Patients resistant to prednisone therapy or dependent on prednisone therapy may benefit from the use of CsA, but the usefulness of cyclophosphamide, azathioprine, or chlorambucil is not clear because there are few randomized prospective studies on which recommendations can be based.

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